Table A1. Clinical Endpoints Identified in the Literature (see following page for definitions and footnotes)

Clinical endpoints identified		MCID definitions
For all adults	**For older adults**	
6 professional consensus statements (Table 2 in CER)*		
• A1c (6 statements) • Hypoglycemia (<70 mg/dL) (6 statements) • Level 2 hypoglycemia (<54 mg/dL) (6 statements) • Time in range (5 statements) • Level 2 hyperglycemia (>250 mg/dL) (5 statements) • Level 1 hyperglycemia (>180 mg/dL) (4 statements) • Time in diabetic ketoacidosis (1 statement) • Coefficient of variation (1 statement)	1 statement†: • A1C • Hypoglycemia (<70 mg/dL) • Level 2 hypoglycemia (<54 mg/dL) A1c not recommended in the presence of very poor health or very complex health conditions	None identified
Clinical Endpoints cited in primary studies; 69 studies, 27 of which enrolled older adults (Appendices B1 and B2 in CER)‡		
Prioritized Clinical Endpoints, Surrogate/Clinical Outcome Domain¶		
• Time in range • Level 1 hypoglycemia (<70 mg/dL) • A1C • Level 1 hyperglycemia (>180 mg/dL)	• Time in range • Level 1 hypoglycemia (<70 mg/dL) • Level 1 hyperglycemia (>180 mg/dL) • Level 3 hypoglycemia (requires assistance, i.e., severe event characterized by altered mental and/or physical status requiring assistance from another person) • A1C	None identified
Clinical Endpoints, Intermediate Endpoints Domain:		
QOL (Life Impact Domain) was the only qualitative endpoint that met selection criteria. Investigated in 40 of 69 studies, 38 times as an exploratory endpoint.	QOL (Life Impact Domain) was only qualitative endpoint that met selection criteria. Investigated in 13 of 27 studies, always as an exploratory endpoint	None identified
Clinical Endpoints, Resource Use Domain		
Healthcare resource use was the only endpoint reported in this domain. 4 of 69 studies investigated once as a secondary endpoint and 3 times as a safety endpoint	Healthcare resource use was the only endpoint reported in this domain. 1 of 27 studies, investigated as a safety endpoint	None identified
Clinical Endpoints, Safety Domain		
• Serious adverse events (13 of 69 studies) • Adverse events (9 of 69 studies)	• Serious adverse events (13 of 27 studies) • Adverse events (9 of 27 studies)	None identified
Other Observations		
• No studies evaluated more than 3 of the 5 endpoints most commonly recommended by professional associations, and few studies evaluated as many as 3 (Table 5 and text in CER). • Differences in volume of citation (p. 15 of the CER) o Level 2 hypoglycemia (<54 mg/dL) more common in T1D than in T2D (39.6% vs 7.7%, p=0.04) o Time in range more common for CLS than for pump or CGM (92% vs 70% vs 57%; p=0.0113) o CLS studies were more likely than pump or CGM studies to use level 2 (p=0.02) or level 3 (p=0.01) hypoglycemia as endpoints o Mean glucose (p=0.01) and diabetic ketoacidosis (p=0.01) more likely in CLS studies than for pump or CGM o **Time in range was the only endpoint to differ in frequency between studies that enrolled older adults (more frequent) than in studies that did not (less frequent) (p=0.01).**		
4 systematic reviews (all meta-analyses) *(Table 6 in CER)*		
Of the key endpoints recommended in the professional consensus statements, A1C, time in range, and severe hypoglycemia were most frequently addressed by systematic reviews.		

Definitions and Footnotes for Table A1

CER, Clinical Endpoints Review; CLS, closed loop systems; CGM, continuous glucose monitoring; QOL, quality of life; T1(2)D, type 1(2) diabetes

*Issued by Advanced Technologies & Treatments for Diabetes Congress (2019), American Association of Clinical Endocrinology (2023), American Association of Clinical Endocrinology (2021), American Association of Clinical Endocrinology (2017), American Diabetes Association (2023), Endocrine Society (2019).
†Issued by Endocrine Society (2019). Full definition of intermediate/complex condition defined in footnote to Table 3 in CER, derived from Table 3 in in LeRoith et al. (the Endocrine Society consensus statement). American Diabetes Association (2023) also advocated not using A1c in patients in very poor health.
‡These endpoints were abstracted from each study: the first 5 primary endpoints, the first 5 clinical secondary endpoints, the first 5 secondary qualitative endpoints, and any resource use or safety endpoints. From those lists, clinical endpoints were prioritized if they accounted for at least 50% of the cumulative number of endpoint citations across studies. All qualitative, resource use, and safety endpoints from those lists are presented here.
¶See Table A2 for the complete selection of physiological/clinical endpoints.

Table A2. All Clinical/Surrogate Endpoints Investigated in Primary Studies

Prioritized endpoints (and thus appear in Table A1) are highlighted.

Endpoint	For all adults (total n, 69 studies)*	For older adults (total n, 27 studies)**
time in range	**49**	**22**
level 1 hypoglycemia (<70 mg/dL)	**35**	**21**
level 1 hyperglycemia (>180 mg/dL)	**34**	**17**
A1c	**34**	**15**
level 3 hypoglycemia (requires assistance of another person)	30	**15**
diabetic ketoacidosis	25	11
mean glucose	18	8
level 2 hyperglycemia (>250 mg/dL)	11	5
level 2 hypoglycemia (<54 mg/dL)	22	10
mean absolute relative difference of device and venous readings (MARD)	5	2
level 3 hyperglycemia (>300 mg/dL)	5	**4**
monitoring frequency	3	0
sensor longevity	2	1
Clarke Error Grid	2	0
glucose variability	2	0
days of CGM use	1	0
current diabetes standards	1	0
diabetic angiopathy markers	1	0

†Issued by Endocrine Society (2019). American Diabetes Association (2023) also advocated not using A1c in patients in very poor health.
NOTE: The Clarke Error Grid evaluates the clinical significance of inaccuracies in blood glucose concentration measurements.

Table B. Surrogate Targets for Percent Time at Different Glucose Levels

Data reviewed in CER	All adults		Older adults	
Goals according to 3 professional consensus statements* *(Table 3 in CER)*	A1c	<7% or individualized	A1c	<7.0-<7.0-<7.5% in healthy older adults, <8% in complex intermediate, do not use in very complex (focus on hypoglycemia)**
	Time in [target glucose] range	>70%	Time in range	>50%
	Level 1 hypoglycemia (<70 mg/dL)	<4%	Level 1 hypoglycemia (<70 mg/dL)	<1%
	Level 2 hypoglycemia (<54 mg/dL)	<1%	Level 2 hypoglycemia (>54 mg/dL)	~0% (a difficult target to meet without assistance of a device)
	Level 1 hyperglycemia (>180 mg/dL)	<25%	Level 1 hyperglycemia (>180 mg/dL)	<10%
	Level 2 hyperglycemia (>250 mg/dL)	<5%	Level 2 hyperglycemia (>250 mg/dL)	<10%
ADA, UK NICE *(text in CER)*	A1C value of >0.5% is accepted as clinically significant			

ADA, American Diabetes Association; NICE, National Institute for Health and Clinical Excellence

*Issued by Advanced Technologies & Treatments for Diabetes Congress (2019), American Association of Clinical Endocrinology (2023), American Association of Clinical Endocrinology (2021)

**complex/intermediate: multiple coexisting chronic illnesses and either two or more impairments in instrumental activities of daily living (managing medication, preparing meals, etc.) or mild-to-moderate cognitive impairment; very complex/poor health: long-term care or end-state chronic illness or moderate-to-severe cognitive impairment or two or more impairments in activities of daily living (bathing, dressing, eating, etc.)

REVIEW QUESTIONS

After reading the full CER and Clinical Endpoints Summary, please be prepared to discuss the following questions in the subcommittee meeting.

1. Do you believe that the search strategy used in the CER is likely to have captured the appropriate literature? (See the "Identifying the Literature" section, starting on page 5 of the full CER).

2. Are the appropriate outcome domains for diabetes management research reflected in the CER findings? (The CER found enpoints in the Clinical, Qualitative, Resource Use, and Safety domains). Are important domains missing, and are omissions likely due to deficiencies in the literature search strategy or omissions in the available body of clinical research literature?

3. Consider the surrogate/clinical endpoints in Table A1 of this document.
    a. Should these be considered key endpoints for studies investigating the use of devices for self-management of diabetes in older adults?
    b. Should additional key endpoints be considered – either endpoints listed in Table A2 or endpoints unrepresented in the CER?
    c. Are the thresholds specified for these endpoints appropriate, e.g., <70 mg/dL as the definition of hypoglycemia?

4. Consider the nonclinical endpoints listed in Table A1.
    a. Which of these should be considered key endpoints for studies investigating the use of devices for self-management of diabetes in older adults?
    b. Should additional nonclinical endpoints be considered?

5. Consider the quality-of-life instruments listed in Appendix Table B3 of the CER. Are these appropriate for studies investigating the use of devices for diabetes self-management in older adults, and are any important instruments missing?

6. Can you offer definitions of a minimal clinically important difference (MCID) for the surrogate/clinical endpoints that you designated to be key endpoints in response to question #3? An MCID is the smallest benefit of value to patients, for example, hypothetically, a 10% reduction in time spent outside an acceptable A1c range. Please keep in mind the typical age of the Medicare population.